Uric Acid Nephrolithiasis: Recent Progress and Future Directions

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The prevalence of urolithiasis has been increasing for the past few decades in industrialized nations. Uric acid calculi account for a significant percentage of urinary stones. Certain risk factors may be involved in the pathogenesis of uric acid nephrolithiasis, including hyperuricosuria, low urinary volume, and persistently low urinary pH. Patients with medical conditions that promote profound hyperuricosuria are at high risk of developing uric acid calculi. These conditions include chronic diarrheal states; myeloproliferative disorders; insulin resistance, including diabetes mellitus; and monogenic metabolic disorders, such as Lesch-Nyhan syndrome. Computed tomography can provide a definitive diagnosis. Except in cases in which there is severe obstruction, progressive azotemia, serious infection, or unremitting pain, the initial treatment of patients with uric acid nephrolithiasis should be medical dissolution therapy because this approach is successful in the majority of cases. A thorough review of the epidemiology and pathophysiology of uric acid nephrolithiasis is crucial for the diagnosis, treatment, and prevention of stones in patients with this condition.

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Urolithiasis has plagued humanity since antiquity, and its prevalence in industrialized nations has been on the rise for the past few decades. Uric acid calculi account for a significant percentage of urinary stones, second only to calcareous stones. Thus, a thorough understanding of the epidemiology and pathophysiology of uric acid nephrolithiasis is crucial for the diagnosis, treatment, and prevention of stones in patients with this condition.

Uric acid is used by reptiles and birds as a means to eliminate excess nitrogen, although for lower mammals it is simply a byproduct of purine metabolism and is excreted in the urine after conversion into allantoin by the enzyme uricase. This enzyme has been lost in the evolution of higher primates, including humans, suggesting that a relative hyperuricemia bestows some survival or reproductive advantage. However, despite these potential benefits, uric acid may be a prime player in some noxious processes such as gout and nephrolithiasis.[1]

The pathogenesis of uric acid nephrolithiasis is incompletely understood. Hyperuricosuria, low urinary volume, and persistently low urinary pH are clearly risk factors, the latter being the most prevalent and important. Almost all patients in whom uric acid calculi develop have persistently acidic urine, and only a small fraction have hyperuricosuria.[1] Despite recent findings suggesting that defects in renal tubular ammonia production and secretion can at least partially explain the observed low urinary pH, the pathophysiology has not been totally elucidated. A gene linked to uric acid stone formation has recently been identified, but its function has not been defined.[2]

Patients with uric acid stones present with a spectrum of symptoms and signs similar to other patients with urinary tract stones, including pain, malaise, nausea, lower urinary tract symptoms, and hematuria. Low urinary pH and a computed tomography scan demonstrating stones with a low attenuation coefficient value should raise diagnostic suspicion for this entity. In addition, patients with conditions that promote profound hyperuricosuria are also at risk of developing these calculi. Therefore, this should be suspected in those with myeloproliferative disorders; insulin resistance, including diabetes mellitus; and monogenic metabolic disorders, such as Lesch-Nyhan syndrome.

Uric acid stones are truly unique in that they dissolve readily in a favorable urinary pH milieu, achievable with oral medical therapy. We present an overview of the pathophysiology of this disorder and the evaluation and management of those afflicted with it.

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Epidemiology

In the United States, the incidence of nephrolithiasis is estimated to be 0.5% per year.[3] The prevalence seems to be on the rise. Comparison of data from the United States National Health and Nutrition Examination Survey (NHANES) II and III showed that the prevalence of stone disease in the general population has increased from 3.8% during 1976 to 1980 to 5.2% during 1988 to 1994 and is similar to that in other industrialized nations.[4] Likewise, its annual economic burden climbed from $1.3 billion in 1994 to more than $2 billion in 2000, despite the introduction of minimally invasive procedures, reductions in length of hospitalization, and the transition of care to the outpatient clinic.[5]

Uric acid nephrolithiasis accounts for approximately 7% to 10% of stones subjected to analysis. The earliest stone composition analyses from the 1960s showed that approximately 10% of all stones were composed of uric acid.[6] In a more recent analysis of stones isolated from patients in the Veterans Administration system, 9.7% were composed solely of uric acid.[7,8] In another large study, uric acid stones accounted for 7% of all stones analyzed.[9] Although these figures may represent an overestimate of the true frequency distribution, they do reflect the significance of this condition.

The frequency of uric acid stones varies with age, gender, geographic location, and local environmental factors. For instance, patients older than 65 years developed uric acid stones at twice the rate of younger patients in a retrospective study of 6000 patients.[10] In another series, males outnumbered females almost by a factor of 3.[11] The difference in the proportion of uric acid stones may also be different among ethnic groups. Portis and associates reported that 50% of Hmong patients with kidney stones had uric acid calculi, as compared with 10% in non-Hmong patients.[12] In another study, the uric acid stone frequency was 6% for whites and 35% for non-whites.[13] This frequency spectrum is also seen among different countries: less than 1% in India, 4% in Sweden, 15% in Japan, 17% in Germany, and up to 40% in Israel.[14-18] Environment may influence uric acid stone formation. A study demonstrated that among stone formers, the prevalence of stone formers was 9% in those factory laborers working in a hot environment, as compared with .9% in those working at standard room temperature. This

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relationship is somewhat of a supposition as stone content was not analyzed in this study.[19]

Uric Acid Metabolism

Nitrogenous waste comes from 2 major sources in animal metabolism: amino acids and purines. Catabolism of amino acids yields ammonia as a byproduct, which is highly toxic in significant concentrations and must either be excreted or metabolized to innocuous compounds such as glutamine and urea for subsequent processing. Excess purines whether from cell turnover, de novo purine synthesis, or dietary sources are ultimately converted into uric acid by a series of enzymes ending with xanthine oxidase. Uric acid is either directly excreted in higher primates or further degraded into allantoin by the enzyme uricase in other species. Some species go several steps further to degrade allantoin into urea and/or ammonia and a salvageable carbon skeleton through reactions catalyzed by the enzymes allantoinase, allantoicase, and ureidoglycolate hydrolase.

Glutamine acts as a substrate for both the urea cycle and de novo purine synthesis and forms a link among these 3 pathways. Indeed their products (ammonia, urea, and uric acid) are all used to eliminate excess nitrogen, although each species uses only 1 pathway to do the majority of the work.

Fish eliminate nitrogen through passive diffusion of ammonia across their gills, whereas other lower animals such as reptiles and birds excrete uric acid in crystalline form. Although it seems foolhardy to expend considerable metabolic energy synthesizing uric acid de novo only to dispose of it, the payoff comes in the form of the water conserved from excretion of solid phase crystals instead of a dilute solution. Mammals on the other hand convert ammonia into urea and excrete it in urine, while reserving uric acid primarily for the elimination of byproducts of purine metabolism.[1]

In higher primates, humans among them, the uricase gene has been completely silenced by a series of nonsense and frameshift mutations in the promoter and coding regions, resulting in a relative hyperuricemia. Humans have concentrations of uric acid more than 10-fold higher than in other mammals.[20] Because nitrogenous waste is sufficiently handled by the urea cycle, the selective loss of uricase in higher primates must confer an evolutionary advantage given the added risk of developing urinary calculi and gout. Although there is evidence suggesting that uric acid has antioxidant,[21-24] neuroprotective,[25-28] immune modulating,[29] and beneficial cardiovascular effects,[30] these claims have not been confirmed as yet.

At physiologic pH, uric acid exists predominantly as urate, its ionized form, unbound to any carrier protein in plasma. Though endogenous production accounts for 300 to 400 mg of urate per day, total excretion can vary greatly depending on dietary purine intake. The kidneys handle 70% of the daily excretion of uric acid with the remainder being eliminated in the gut, skin, hair, and nails.[31] In the gut, bacteria degrade uric acid into carbon dioxide and ammonia, which are either reabsorbed or released as intestinal gas. Despite being completely filtered at the glomerulus, the fractional excretion of uric acid is only about 10%, indicating that the balance between renal tubular secretion and reabsorption regulates the total amount of uric acid cleared by the kidney.[32,33] Nearly 99% of the filtered load of uric acid is reabsorbed in the S1 segment of the proximal tubule by the recently identified urate transporter URAT1, encoded by the gene *SLC22A12*.[34] Urate secretion occurs in the S2 segment via the organic acid transporters (OAT1 and OAT3) as well as a selective urate transporter, URAT. Post-secretory reabsorption of urate occurs in the S3 segment and is also mediated by URAT1.[35]

Pathophysiology

Stone formation is a dynamic process that involves both biochemical derangements of urine that promote crystal nucleation, aggregation, and possibly adhesion. The role of Randall's plaque in the development of calcium oxalate stones has been elegantly demonstrated by the studies of Evan and associates, who analyzed renal tissue obtained during percutaneous nephrolithotomy.[36-38] However, such anatomic studies have not been reported for uric acid stone formers.

Urinary abnormalities that predispose to formation of uric acid calculi include persistently low urinary pH (the most important factor), dehydration with its surrogate marker of low urinary volume, and hyperuricosuria (defined as 24-hour urinary uric acid exceeding 750 mg/d in women and 800 mg/d in men[39]). The etiologies of these derangements are wide and varied and are presented in Table 1.

Persistently Low Urinary pH

It has been known for years that persistently low urine pH is closely associated with uric acid nephrolithiasis, although the primacy of its importance has only recently been recognized.[11,40,41] Almost all of those who form uric acid stones have persistently low urinary pH, and most excrete normal amounts of uric acid. Patients who lack congenital or acquired conditions to explain the development of uric acid stones are said to have idiopathic uric acid nephrolithiasis or "gouty diathesis." These 2 interchangeable terms describe

Table 1
Causative Factors for Uric Acid Stone Formation

	Low Urinary Volume	Low Urinary pH	Hyperuricosuria
Idiopathic or gouty diathesis		X	
Obesity		X	
Insulin resistance		X	
Animal protein in diet		X	X
Primary gout		X	X
Chronic diarrhea	X	X	
Dehydration	X		
Lesch-Nyhan syndrome			X
Von Gierke disease			X
Disorders of high cell			X
Turnover			
Neoplasias			
Sickle cell disease			
Hemolytic anemias			
Polycythemia vera			
Psoriasis			
Renal hyperuricosuria			X
Familial hyperuricosuria			
Fanconi syndrome			
Hartnup disease			
Wilson's disease			

a syndrome that may be related to primary gout and characterized by hyperuricemia, diminished fractional excretion of uric acid, and persistently low urinary pH.[40]

The critical role of low urinary pH in the formation of uric acid stones can best be explained with fundamental acid-base chemistry and the marginal solubility of uric acid. When dissolved in water the nitrogen at position N9 of urate can accept a free proton to form uric acid, represented by the following equation:

$$\text{Urate} + H^+ \leftrightarrow \text{Uric Acid}$$

The first acid dissociation constant (pKa) of this reaction is 5.5; the second pKa has no physiological significance.[42] In aqueous solutions at 37°C uric acid has a solubility constant (K_{sp}) of approximately 100 mg/L, whereas urate is 20 times more soluble.[43] At a pH equal to the pKa, uric acid and urate exist in equal proportions as a consequence of the Henderson-Hasselbach equation. Hence, if 200 mg of urate were introduced into a 1-L aqueous solution with a pH of 5.5 at 37°C, 100 mg would become uric acid and the remainder would continue to be urate. In contrast, if 1200 mg of urate were instilled into a similar volume at a pH of 6.5, 1100 mg would remain in the soluble urate form. These relationships are based on the upswing of the uric acid dissociation curve at this pH, which plateaus at a pH of approximately 7.2. Thus, patients with normal uric acid excretion but a low urinary pH can develop uric acid stones, whereas those with a normal or higher urinary pH but excessive urate excretion will not.

The exact mechanism of persistently acidified urine seen in patients with uric acid stones remains uncertain. However, a number of different hypotheses have been proposed. A comparison between subjects with idiopathic uric acid nephrolithiasis and normal subjects, both on controlled diets, showed that uric acid stone formers not only had consistently acidic urine, but they also excreted less of their acid burden in the form of ammonium, relying instead on a higher level of titratable acid excretion. Additionally, these patients have a blunted response to ammonium chloride oral acid loading as evidenced by excreting urinary ammonium in quantities 7-fold less than those in normal subjects. These observations led some to theorize that these patients possess a defect in ammonium excretion, leading to the loss of an important urinary buffer without which small increases in the concentration of H^+ would dramatically lower pH.[44,45]

Some investigators have suggested that defects in the enzymes glutaminase and/or glutamate dehydrogenase, which metabolize glutamine into ammonia and α-ketoglutarate, may cause impaired ammonium secretion. Furthermore, they hypothesize that diminished consumption of glutamine in this pathway would shift it to other pathways that consume glutamine, namely de novo purine synthesis, leading to hyperuricemia. These 2 hypotheses are supported by the observation that subjects with uric acid nephrolithiasis have elevated

plasma levels of glutamate and, when given ^{15}N-labeled glycine, incorporated more ^{15}N into uric acid than ammonium compared with controls.[46,47] Other investigators, however, have found no discernible difference between renal glutaminase activity of subjects with gout and those without.[48] The role of glutamine dehydrogenase has been for the most part unexplored. Thus, the exact role of renal glutamine catabolism in causing insufficient urinary ammonium secretion is unclear at this point.

Not only does pH need to be low to form uric acid stones, but it also must remain persistently low. Non-stone formers occasionally develop urine acidic enough to precipitate crystals despite normal concentrations of uric acid, although it is thought that transient alkalinization of urine that occurs with meals halts the progression to bona fide stones. This theory is supported by the idea that periodic urinary alkaline tides dissolve away any uric acid crystals that have formed as a result of transiently acidic urine.[49,50] The primary defect for this absence of alkaline tides can theoretically occur at several places: defective gastric acid secretion, decreased glomerular filtration rate leading to decreased filtered load of bicarbonate, and increased renal tubular reabsorption of bicarbonate. Because no data exist indicating that gastric acid secretion is impaired, failure to produce the physiologic urinary alkaline tide is suspected to result from a renal defect, the nature of which remains uncertain.[51] Although some have questioned the existence of physiologic alkaline tides, patients with uric acid stones clearly lack variation in their urinary pH compared with normal subjects.[52-56] Whatever its cause, the existence of persistently low urinary pH has clearly been established as a risk factor for uric acid nephrolithiasis.

Hyperuricosuria

Interestingly patients with hyperuricosuria but normal urinary pH also develop stones, although these are often mixed stones composed of calcium oxalate and urate. Although urate is many times more soluble than uric acid, it is not infinitely so. At high enough concentrations monosodium urate precipitates out of solution and is hypothesized to cause calcium oxalate crystallization by heterogenous nucleation, the attenuation of macromolecular inhibitors of lithogenesis, or a salting-out phenomenon.[39,57,58] Hyperuricosuria is most commonly caused by dietary indiscretion, though mutations in the URAT1 channel can cause congenital renal hypouricemic hyperuricosuria.[34]

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Low Urinary Volume

Decreased urinary output results in increasing concentrations of lithogenic solutes in the urine. Because the solubility of uric acid is limited, high enough concentrations of urate may cause uric acid precipitation as well as monosodium urate precipitation. The observation that uric acid stones occur in the tropics and hot environments supports this hypothesis.[59-61]

Macromolecular Inhibitors of Crystallization

It has been known for decades that urine contains factors that inhibit crystal formation. Despite years of extensive investigation, little is understood about how these factors modulate uric acid crystallization and stone formation. In vitro studies demonstrated inhibitory effects of glycoproteins, glycosaminoglycans (GAGs), and surfactants found in urine on uric acid crystallation.[62] A recent study of a genetically and geographically isolated cohort showed that uric acid formers excreted significantly lower levels of GAGs.[63] However, the exact role that deficiency in such inhibitors plays in uric acid stone formation is not defined.

Genetic Factors

The familial predisposition to form urinary stones is well established, although for the most part it is clearly a multifactorial condition influenced by both genetic and environmental factors.[64] In the past few years, the *ZNF365* gene on chromosome 10q21-q22 was discovered to be associated with uric acid nephrolithiasis. Although this gene encodes for 4 different proteins through alternate splicing, only 1 predisposes to the development of uric acid stones. The functions of these gene products have not been elucidated. A homologue for this gene is not detectable in mice; in Old World and New World monkeys, it exists as an unexpressed gene. It seems that this novel gene surfaced in

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the Miocene era around the time that primates lost the function of uricase. It is possible that the product of this gene protects against the harmful effects of hyperuricemia due to silencing of the uricase gene without losing its beneficial effects. It will be interesting in the years to come to determine what the products of this gene do in the body and how they affect the pathophysiology of uric acid nephrolithiasis. However, until this gene's function is characterized, any attempt at explanation is purely conjectural.

Overview of Etiologies

Idiopathic Uric Acid Nephrolithiasis

Patients who have no identifiable congenital or acquired cause for the metabolic derangements that predispose them to developing uric acid stones are said to have idiopathic uric acid nephrolithiasis or gouty diathesis. The term *gouty diathesis* was historically used to classify patients with hyperuricemia, decreased fractional excretion of uric acid, low urinary pH, and latent gout. Patients with isolated low urinary pH in association with uric acid stones are also grouped into this category on the basis of the a priori assumption that they may have an early form of gout that will eventually develop into gouty arthropathy.[57]

Primary Gout

Most patients with primary gout have hyperuricemia secondary to impaired renal excretion of uric acid, whereas only a minority present with increased production. And although patients with gout can present with both painful arthropathies and urolithiasis, the incidence of uric acid stones in this population only ranges from 10% to 20%.[65] Along with abnormalities in renal uric acid handling, this group also demonstrates acidic urinary pH, which again is thought to be the driving mechanism for uric acid stone formation.

Chronic Diarrhea

Patients with chronic diarrhea or other forms of gastrointestinal bicarbonate loss are at risk for developing uric acid nephrolithiasis. For example, patients with inflammatory bowel disease as well as those with ileostomies have an increased risk of forming both uric acid and calcium oxalate kidney stones. The mechanism of uric acid stone formation in these patients is attributed to hypovolemia, which increases the supersaturation of these salts and chronic gastrointestinal loss of bicarbonate leading to more acidic urine.[66,67]

Insulin Resistance

In recent years, a link between uric acid stone formation and insulin resistance has been established.[68] A prime example is patients with gouty diathesis who have features of insulin resistance and the metabolic syndrome, such as hyperglycemia, hypertriglyceridemia, and obesity.[40] More than half of subjects with uric acid calculi have been found to have insulin resistance.[45] Diabetic stone formers are almost 6-fold more likely to develop uric acid stones than non-diabetic stone formers.[69] A study has demonstrated that urinary pH inversely correlates with body weight.[70] In contrast, urinary pH is positively correlated to insulin sensitivity.[71] Physiologic experiments have shown that acute surges in insulin elevate urinary pH by stimulating proximal renal tubular ammoniagenesis by increasing catabolism of glutamine into 2 molecules of ammonia and α-ketoglutarate[72] as well as the activity of the sodium/hydrogen ion exchanger 3 (NHE_3) that secretes and traps ammonia in the urinary space as ammonium.[73,74] In some animal models elevated levels of free fatty acids (often observed in insulin-resistant states) increase levels of acetyl-CoA, which competes with α-ketoglutarate for entry into the Krebs cycle. Decreased metabolism α-ketoglutarate leads to its accumulation and in turn impedes the catabolism of glutamine by the mass-law effect, effectively reducing ammoniagenesis.[75-77]

Dietary Excess

Patients who consume high quantities of meat are at risk for forming uric acid stones because of the increased purine load and acid-ash content of animal protein. This promotes hyperuricosuria and a mild metabolic acidosis resulting in a lowering of urinary pH. Therefore, dietary measures may help to prevent uric acid stone formation.[78]

Neoplastic Disorders

Those with myeloproliferative disorders and malignancy may have elevated levels of uric acid in the blood from rapid cell turnover and tumor necrosis, especially in the setting of chemotherapy. Along with the electrolyte abnormalities that occur during tumor lysis, massive hyperuricemia and hyperuricosuria may occur, leading to urate nephropathy. Other conditions associated with a higher incidence of uric acid nephrolithiasis include conditions with high cell turnover, such as sickle cell disease, hemolytic anemias, polycythemia vera, and psoriasis.[79,80]

Renal Hyperuricosuria

Several renal diseases are associated with hyperuricosuria and uric acid nephrolithiasis, including Fanconi syndrome, Hartnup disease, Wilson's disease, and familial hypouricemic hyperuricosuria. These conditions predispose patients to renal wasting of uric acid. The identification of the uric acid transporter URAT1 was a breakthrough in our understanding of urate handling by the nephron, and it is the transporter that is defective in

familial hypouricemic hyperuricosuria.[34] To date, 11 different loss-of-function mutations have been identified in this gene within this cohort.[81]

Congenital Hyperuricemia

Inborn errors of metabolism, such as hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency and type 1 collagen storage disease, can both cause uric acid stones because they cause hyperuricemia and hyperuricosuria. HGPRT deficiency results in a failure to salvage purines from cell break down, leading to severe hyperuricemia. This condition is X-linked recessive and in its most severe form, Lesch-Nyhan syndrome, is characterized by mental retardation, gout, uric acid nephrolithiasis, and self-mutilation.[82] Type 1 collagen storage disease, also known as von Gierke disease, is an autosomal recessive defect in glucose-6-phosphatase and affected patients have hypoglycemia, hyperlactacidemia, and hyperuricemia.[83]

Diagnosis

Patients with uric acid calculi have symptoms and signs similar to those with other types of stones, which include flank and abdominal pain, nausea, emesis, lower urinary tract symptoms, hematuria, and gonadal pain in males. Therefore, existence of general clinical predictors for the presence of stones should prompt one to assess for such a diagnosis. In a multivariate logistic regression analysis the combination of acute abdominal pain of recent onset ($\leq$ 12 hours) without changes in appetite, loin or costovertebral tenderness, and hematuria (red blood cells $>$ 10 high-power fields) has a sensitivity of 80% and specificity of 99% for detecting nephrolithiasis.[84]

A careful medical history should be obtained in patients suspected of having a stone event, including a query for underlying disease processes that are associated with stone formation, such as gastrointestinal problems, especially those in which malabsorption and diarrhea exist; conditions with high cell turnover, such as malignancy or myeloproliferative disorders; congenital conditions associated with hyperuricosuria; and insulin resistance. A careful family history for presence of the aforementioned disorders and nephrolithiasis should be elicited (Table 1).

Certain baseline laboratory studies should be obtained. Uric acid stones should be suspected in any patient with a persistently low urinary pH, less than 5.5, and the radiographic findings reviewed subsequently. Therefore, urinalysis is an important part of the evaluation process. Serum blood urea nitrogen and creatinine, electrolytes, and uric acid should be determined when this diagnosis is considered.

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The preferred radiographic modality for initial evaluation of patients with suspected renal colic is non–contrast-enhanced computed tomography, which has 96% sensitivity, 99% specificity, 97% negative predictive value, and 98% positive predictive value for stone detection.[85] Given that uric acid calculi are usually radiolucent on abdominal radiographs, computed tomography possesses special importance in the evaluation of uric acid nephrolithiasis.[86] Measurement of the computed tomography attenuation values of the stones may also assist in the diagnosis as these stones have Hounsfield values of 200 to 400 units.[87] Other radiolucent stones with low attenuation values include those composed of matrix, ammonium urate, 2,8-dihydroxyadenine, hypoxanthine, and xanthine, and stones composed of certain drugs or their metabolites. Renal ultrasonography can be used to detect these stones and may be a good method to follow patients with a history of uric acid stones or those who are actively being treated.

Stone analysis is used to confirm the diagnosis of uric acid nephrolithiasis. Uric acid stones may exist in the following forms: anhydrous form, the most common; dihydrate; and monosodium urate. Ammonium acid urate stones are another type of urate stone. Because the underlying pathophysiology and treatment approaches are somewhat different, this stone type will not be addressed in this review.

Treatment

Except in cases in which there is severe obstruction, progressive azotemia, serious infection, or unremitting pain, the initial management of patients with uric acid nephrolithiasis should be medical dissolution therapy because this approach is successful in the majority of cases (70% to 80%).[88,89] Patient noncompliance or the intolerance of the prescribed medications are the typical causes for medical therapy failure. The goals of medical therapy address the 3 biochemical defects that lead to stone formation: acidic urinary pH, hyperuricosuria, and low urinary volume.

Acidic Urinary pH

Urinary pH manipulation has been used for centuries to dissolve uric acid stones. Michelangelo himself drank

mineral water to dissolve his kidney stones while under the care of the great surgeon Realdo Colombo in the mid-16th century. Remarkably, the same water is marketed today in Italy under the brand name Fiuggi and is purported to benefit patients with stones.[90]

The goal of pH manipulation therapy is to maintain a urinary pH of 6.5 to 7.0. Patients should use pH paper to monitor urine pH. Adjustments in the doses of the prescribed medication can be made by the patient in concert with the treating physician based on clinical response and the urinary pH levels. It is important that urinary pH is not maintained above this range because this places the patient at risk for developing calcium phosphate stones.[91,92] Although the administration of intravenous agents such as lactate (because of its conversion to bicarbonate) or sodium bicarbonate has been used for this purpose, this approach, which is infrequently used as oral therapy, is quite effective.[91,93] Potassium citrate is the preferred agent and generally a dose of 15 to 30 mEq administered twice daily in adults will achieve the aforementioned pH goal. This agent is preferred over sodium salts because monopotassium urate is more soluble than monosodium urate. In addition, this avoids the increase in calcium excretion and reduction in citrate excretion associated with sodium loading. However, certain patients are not candidates for potassium citrate therapy owing to diminished renal function or high baseline serum potassium levels. Some patients are also intolerant of the associated gastrointestinal side effects of potassium citrate. Sodium bicarbonate or sodium citrate are the preferred agents in this setting. The former also has the advantage of limited cost. However, the sodium-based salts must be used with caution in those with congestive heart failure or poorly controlled hypertension. The usual adult dose of sodium bicarbonate is 650 to 1000 mg 3 to 4 times daily. Commercial baking soda is a source of sodium bicarbonate, and the usual adult dose is 1 to 2 teaspoons 3 to 4 times daily.[79] Acetazolamide was once used for pH manipulation but is not recommended for routine use because it reduces citrate excretion and promotes calcium excretion.[94,95] In addition, the concomitant consumption of citrus fruits and juices may further help increase urinary pH.[89,96-98] Contact chemolysis by local irrigation of the collecting system with alkaline solutions such as sodium bicarbonate (pH 7-9), tromethamine (pH 8.6), and tromethamine-E (pH 10.5) was used to dissolve uric acid stones. However, the efficacy of oral therapy and success of minimally invasive stone-removing procedures has relegated this approach to historic archives.[95]

Hyperuricosuria

Twenty-four-hour urine testing should be undertaken if a hyperuricosuric state is suspected. When hyperuricosuria is identified, the underlying cause of this abnormality should be addressed if possible. Because the most common cause is purine gluttony, patients should first be counseled to avoid foods rich in purine such as red meat, fish, poultry, beer, and legumes. Not only do these foods increase the uric acid load that the kidneys must excrete, but also digestion of animal protein produces a transient metabolic acidosis that lowers urinary pH.[99] A recent trial showed both urinary pH and uric acid concentration were significantly reduced in subjects consuming a balanced diet of vegetables and moderate amounts of animal protein and purines when compared with subjects consuming a typical Western diet.[100] Patient compliance with dietary modifications can be monitored by measuring urinary urea and sulfate indexed to creatinine.[101]

Patients who fail to respond to dietary changes or require immediate reduction in uric acid burden (ie, symptomatic hyperuricemic conditions such as gout, hyperuricosuric calcium urolithiasis, and urate nephropathy) should be given allopurinol, a competitive inhibitor of xanthine oxidase. This enzyme catalyzes the conversion of hypoxanthine into xanthine and xanthine into urate. The usual dose range for adults is 100 to 300 mg/d. In the patient with renal insufficiency, it must be dosed based on estimated creatinine clearance.[102] Adverse reactions include gastrointestinal upset, precipitating acute gout attacks, Stevens-Johnson syndrome, and the potentially fatal allopurinol hypersensitivity syndrome characterized by fever, rash, hepatitis, eosinophilia, and acute renal failure.

Allopurinol and its active metabolite oxypurinol not only act as purine analogues, but they also reduce de novo purine synthesis by enhancing salvage by HGPRT. However, in patients with myeloproliferative disorders, tumor lysis, and HGPRT deficiency, treatment with allopurinol can cause significant xanthinuria and the formation of xanthine stones.[103] Rarely, oxypurinol may form urinary stones.[104] Recently, recombinant pegylated uricase has been used in the treatment of tumor lysis, and it may eventually be useful in patients where allopurinol is contraindicated or not fully effective.[105]

Low Urinary Volume

Because low urinary volume leads to increased concentrations of uric acid, it is important to maintain a urinary volume of at least 2 to 2.5 L per day. This is most effectively accomplished with vigorous hydration. Further, hydration to compensate for periods of

high stone-forming potential such as after meals, during physical activity, or during sleep has been theorized to be important.[43] Dipstick testing to assess specific gravity may be used to prompt compliance with fluid therapy in this cohort.

Surgical Management

A stone-removing procedure may be needed in patients who do not respond to dissolution therapy or have complicating features, such as prolonged urinary obstruction, sepsis, or unremitting pain. Uric acid stones are amenable to all modalities of lithotripsy. In a recent series of 443 patients with uric acid stones, 88.5% were stone-free 3 months after shock-wave lithotripsy and postoperative pH manipulation therapy. Better success was observed with stones smaller than 20 mm and those that were visualized well on ultrasound and situated in the renal pelvis.[106] The administration of intravenous contrast material or installation of contrast material through a nephrostomy tube or externalized ureteral stent can be used to direct shock wave focusing when fluoroscopic-based lithotripters are used. These stones can be removed effectively with ureteroscopy and percutaneous nephrolithotomy. These are mainly assigned based on stone volume but other patient factors may influence treatment choices. Holmium yttrium-aluminum-garnet (Holmium:YAG) laser lithotripsy is highly effective at fragmenting these stones.[107] Although in vitro studies have demonstrated that cyanide is produced when uric acid stones are fragmented with Holmium:YAG lasers, there have been no reported cases of cyanide toxicity.[108,109]

Patient Follow-Up

Patients with uric acid stones who are undergoing dissolution therapy need to be observed closely to ensure that stone reduction is occurring and that prolonged renal obstruction does not develop. Renal ultrasonography is an excellent method to observe these patients. Repeat non–contrast-enhanced computed tomography imaging may be necessary to confirm success or failure. In addition, serum electrolytes, blood urea nitrogen, and creatinine should be monitored with pH manipulation therapy and liver enzymes should be checked when allopurinol is prescribed. Patients should be maintained on these medications chronically after successful stone dissolution or removal unless the underlying risk factors for uric acid stone formation have been reversed. Again, renal ultrasonography is the ideal modality for long-term follow-up in this cohort because it is reasonably sensitive for stone detection, is devoid of ionizing radiation, and is highly sensitive for detection of hydronephrosis. Computed tomography can be ordered when clinically indicated.

Future Directions

The past few years have seen great strides in our understanding of uric acid nephrolithiasis, particularly in understanding the mechanisms of the persistently low urinary pH seen in this cohort. The identification of the urate transporter URAT1 as well as the discovery of the *ZNF365* gene associated with uric acid nephrolithiasis foreshadows many more exciting discoveries to come. However, much remains to be revealed as we only have the beginnings of a unified model for this multifactorial condition. In addition, defining the molecular defects that cause insufficient ammoniagenesis or ammonium secretion in these patients will perhaps foster the development of better treatment strategies. In addition, a search for anatomic correlates within the kidney may provide important insights. ■

Main Points

- A thorough understanding of the epidemiology and pathophysiology of uric acid nephrolithiasis is crucial for the diagnosis, treatment, and prevention of stones in these patients.
- The pathogenesis of uric acid nephrolithiasis involves hyperuricosuria, low urinary volume, and persistently low urinary pH, the latter being the most prevalent and important.
- Other causes of stone formation include chronic diarrhea, primary gout, insulin resistance, excess purine in the diet, neoplastic disorders, renal hyperuricosuria, and congenital hyperuricemia.
- The preferred radiographic modality for initial evaluation of patients with suspected renal colic is non–contrast-enhanced computed tomography.
- Except in cases in which there is severe obstruction, progressive azotemia, serious infection, or unremitting pain, the initial management of patients with uric acid nephrolithiasis should be medical dissolution therapy because this approach is successful in the majority of cases.

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